VOLUME 30 · NUMBER 27 · SEPTEMBER 20 2012

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Male Reproductive Health After Childhood, Adolescent, and Young Adult Cancers: A Report From the Children's Oncology Group

Lisa B. Kenney, Laurie E. Cohen, Margarett Shnorhavorian, Monika L. Metzger, Barbara Lockart, Nobuko Hijiya, Eileen Duffey-Lind, Louis Constine, Daniel Green, and Lillian Meacham

Lisa B. Kenney, Laurie E. Cohen, and Eileen Duffey-Lind, Dana-Farber Cancer Institute and Children's Hospital Boston, Boston, MA; Margarett Shnorhavorian, Seattle Children's Hospital, Seattle, WA; Monika L. Metzger and Daniel Green, St Jude Children's Research Hospital, Memphis, TN; Barbara Lockart, Children's Memorial Hospital; Nobuko Hijiya, Northwestern University, Chicago, IL; Louis Constine, University of Rochester Medical Center, Rochester, NY; and Lillian Meacham, Emory University, Atlanta, GA.

Submitted August 4, 2011; accepted March 19, 2012; published online ahead of print at www.jco.org on May 29, 2012.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: Lisa B. Kenney, MD, Dana-Farber Cancer Institute, 450 Brookline Ave, D321, Boston, MA 02215; e-mail: lisa_kenney@DFCI.harvard.edu.

0732-183X/12/3027-3408/$20.00

DOI: 10.1200/JCO.2011.38.6938

ABSTRACT

The majority of children, adolescents, and young adults diagnosed with cancer will become long-term survivors. Although cancer therapy is associated with many adverse effects, one of the primary concerns of young male cancer survivors is reproductive health. Future fertility is often the focus of concern; however, it must be recognized that all aspects of male health, including pubertal development, testosterone production, and sexual function, can be impaired by cancer therapy. Although pretreatment strategies to preserve reproductive health have been beneficial to some male patients, many survivors remain at risk for long-term reproductive complications. Understanding risk factors and monitoring the reproductive health of young male survivors are important aspects of follow-up care. The Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancer (COG-LTFU Guidelines) were created by the COG to provide recommendations for follow-up care of survivors at risk for long-term complications. The male health task force of the COG-LTFU Guidelines, composed of pediatric oncologists, endocrinologists, nurse practitioners, a urologist, and a radiation oncologist, is responsible for updating the COG-LTFU Guidelines every 2 years based on literature review and expert consensus. This review summarizes current task force recommendations for the assessment and management of male reproductive complications after treatment for childhood, adolescent, and young adult cancers. Issues related to male health that are being investigated, but currently not included in the COG-LTFU Guidelines, are also discussed. Ongoing investigation will inform future COG-LTFU Guideline recommendations for follow-up care to improve health and quality of life for male survivors.

J Clin Oncol 30:3408-3416. © 2012 by American Society of Clinical Oncology

INTRODUCTION

Curative therapy for cancer during childhood, adolescence, and young adulthood can adversely affect all aspects of male reproductive health. The potential for abnormal development, infertility, and sexual dysfunction is a source of significant emotional distress for survivors.[1-3] Recognizing treatment-associated risks and educating survivors and providers about potential reproductive complications is a key component of follow-up care. The Children's Oncology Group (COG) developed clinical practice guidelines to aid the assessment of survivors of childhood and adolescent cancers for long-term complications.[4,5] The COG Long-Term Follow-Up Guidelines for Survivors of Pediatric, Adolescent, and Young Adult Cancer (COG-LTFU Guidelines) are evidence-based guidelines indexed by therapeutic exposure, which are updated every 2 years according to task force recommendations derived from literature review and expert consensus.[6] In this review, the COG-LTFU Guidelines male health task force presents an overview of male reproductive complications including hypoandrogenism, precocious puberty, reduced fertility, and sexual dysfunction. Risk factors, clinical assessment, and interventions for each of the treatment-associated complications, as put forth in the guidelines, are discussed. In addition, controversial or investigational topics related to male health currently not incorporated in the COG-LTFU Guidelines, but warranting additional consideration, are presented.

HYPOANDROGENISM

Pubertal development and the maintenance of male secondary sexual characteristics depend on adequate production of testosterone by testicular Leydig cells. Inadequate testosterone production—hypoandrogenism—also increases the risk of osteoporosis and metabolic disorders

associated with chronic disease.[7,8] Gonadotoxic chemotherapy, testicular radiation, orchiectomy, and cranial surgery or radiation involving the hypothalamic-pituitary-gonadal (HPG) axis can result in hypoandrogenism (Table 1). Testicular Leydig cells are relatively resistant to treatment toxicity, compared with testicular germ cells, such that survivors who are azoospermic after gonadotoxic therapy may maintain adequate testosterone production.[9-11]

Risk Factors

Primary hypoandrogenism—testicular failure—can result from treatment with high-dose alkylating agents, testicular irradiation $\geq$ 20 Gy, orchiectomy, or combinations of these modalities.[9-17] Treatment-associated risk factors for central hypoandrogenism include surgical disruption of the HPG axis and cranial radiation dose $\geq$ 30 Gy.[15,18,19] Increasing intensity of therapy is associated with increasing risk for hypoandrogenism. Adequate testosterone production is usually maintained after nonmyeloablative doses of alkylating agents and testicular irradiation $<$ 20 Gy; however, subclinical Leydig cell insufficiency (low normal testosterone, elevated serum luteinizing hormone [LH]) can be observed after moderate-dose alkylating agent therapy (cumulative cyclophosphamide $\geq$ 20 gm/m^2)[11,14] or lower total dose of testicular irradiation ($<$ 14 Gy).[9,13,20-24] Similarly, survivors who undergo unilateral orchiectomy and are not exposed to additional gonadotoxic therapy usually maintain adequate testosterone production[25,26]; however, an increased risk of subclinical Leydig cell insufficiency has been reported in survivors of testicular cancer treated with orchiectomy only.[26] Testicular cancer is associated with hypoandrogenism, independent of treatment,[16] and pretreatment hypoandrogenism or microlithiasis in the remaining testis is predictive.[16] Pubertal status is a risk factor for radiation-associated gonadotoxicity. Hypoandrogenism is consistently observed after a testicular radiation dose $\geq$ 24 Gy when survivors are treated before puberty[20,22,23] and not until a testicular dose $\geq$ 30 Gy when survivors are treated postpuberty.[13,20] In contrast, pubertal status is not protective of chemotherapy-associated gonadotoxicity.[10,11]

It should be noted that the dose of gonadotoxic therapy that impairs testicular function varies among individuals; therefore, any survivor treated with gonadotoxic agents is at risk for hypoandrogenism. In addition, because deterioration in testicular function is associated with normal aging, young men treated with gonadotoxic agents are likely to remain at risk for hypogonadism as they reach older adulthood.[7,21,24]

Assessment

Delayed or arrested puberty is the clinical manifestation of hypoandrogenism in survivors treated before or during pubertal development. Pubertal onset in boys normally occurs between ages 9.5 and 13.5 years, beginning with testicular enlargement (testicular volume $\geq$ 4 mL).[27] For survivors treated with gonadotoxic therapy before the onset of puberty, the COG-LTFU Guidelines recommend annual assessment of pubertal development until sexual maturity using Tanner staging, with testicular volume determined by Prader orchidometer (Table 1). Assessment of puberty may be difficult given that boys who receive gonadotoxic therapy can have testicular volumes smaller than expected for age as a result of testicular germinal aplasia,[28] and the development of pubic hair can be mediated by adrenal androgens.[29] Increase in size of the testes beyond 3 mL and scrotal thinning, along with progressive increases in serum testosterone, likely indicate onset of puberty. If puberty does not begin by age 14 years, or puberty does not progress after onset, evaluation by an endocrinologist is recommended.

Young men and adolescents treated with gonadotoxins after completing puberty should be monitored annually for symptoms of androgen deficiency including decreased libido, decreased spontaneous erections, gynecomastia, loss of body hair, reduced muscle bulk, hot flashes/sweating, and reduced testicular volume.[15,30] Symptoms of hypoandrogenism may be nonspecific, so providers should have a low threshold to evaluate survivors with known treatment-associated risks.

Boys presenting with delayed puberty and those at risk for treatment-associated hypoandrogenism are recommended to have measurement of baseline early-morning serum testosterone and gonadotropin levels at age 14 years. Men who are symptomatic or have treatment-associated risk factors for testosterone deficiency are also evaluated by obtaining early-morning serum testosterone and gonadotropin levels (Table 1). In adults, a low morning testosterone level is considered diagnostic of hypoandrogenism.[30] Males with primary testicular failure typically have low testosterone and elevated LH, and males with impairment of the HPG axis will have low testosterone and low or inappropriately normal LH. Low serum testosterone levels can be observed in the absence of elevated LH measurements, so LH should not be used to diagnose androgen deficiency in this population.[7,24] Survivors who are diagnosed with hypoandrogenism should also be evaluated for associated morbidities including low bone mineral density and metabolic syndrome.[8]

Treatment

If screening confirms the diagnosis of hypoandrogenism in an adolescent survivor with delayed or arrested puberty, the decision to begin treatment should be guided by an endocrinologist. Standard treatment for delayed or arrested puberty related to primary testicular failure is administration of increasing doses of testosterone derivatives by either depot intramuscular injection or with *trans*-dermal patch or gel.[28,31] Although testosterone replacement therapy will cause virilization, it has no effect on testicular maturation and can, in fact, inhibit spermatogenesis.

For postpubertal survivors with hypoandrogenism, the goal is to raise serum testosterone levels and sustain them in the midnormal range. Survivors receiving testosterone replacement therapy should be monitored for adverse effects including polycythemia, dyslipidemia, and liver dysfunction; older adults should also be monitored for prostatic hypertrophy. In some clinical settings, pulsatile gonadotropin-releasing hormone (GnRH) delivered via pump is used as an alternative to testosterone replacement therapy in survivors with central hypogonadism and intact pituitary function, resulting in testicular maturation and stimulation of spermatogenesis.[31,32] Similarly, in cases of central hypogonadism with abnormal pituitary function, human chorionic gonadotropin can be used to stimulate androgen production and recombinant follicle-stimulating hormone (FSH) used to stimulate spermatogenesis.[31,33]

Additional Considerations

The benefit of androgen replacement therapy for survivors with symptoms of androgen deficiency and the diagnosis of subclinical Leydig cell insufficiency remains controversial. Studies have demonstrated an association between clinical manifestations of androgen

Table 1. Risk Factors for and Assessment and Evaluation of Male Reproductive Complications After Treatment for Childhood, Adolescent, and Young Adult Cancers

Complication	Therapy	Risk Factors	Assessment	Evaluation
Hypoandrogenism: • Delayed/arrested puberty • Low testosterone	**Alkylating agents:** • Busulfan • Carmustine (BCNU) • Chlorambucil • Cyclophosphamide • Ifosfamide • Lomustine (CCNU) • Mechlorethamine • Melphalan • Procarbazine • Thiotepa • Carboplatin • Cisplatin • Dacarbazine (DTIC) • Temozolomide **Radiation:** ≥ 20 Gy: • Testes • Pelvis ≥ 30 Gy: • Cranial-neuroendocrine axis • Orbital/eye • Ear/infratemporal • Nasopharyngeal • Waldeyer's ring Other fields combined with alkylating agents: • Flank/hemiabdomen • Whole abdomen • Inverted Y, TLI • Prostate/bladder • Iliac/inguinal/femoral • TBI **Surgery:** • Orchiectomy • Hypothalamic pituitary axis	**Treatment factors:** • Higher cumulative doses or combinations of alkylators • Chemotherapy combined with radiation to: abdomen/pelvis, testes, neuroendocrine axis • Younger age at treatment **Host factors:** • Individual variation in cumulative dose that results in hypoandrogenism • Spermatogenesis is impaired at lower doses compared with testosterone synthesis • Prepubertal status does not protect against testicular toxicity	**History:** • Puberty (onset, tempo) • Sexual function (erections, nocturnal emissions, libido) **Examination:** • Tanner staging • Testicular volume by Prader orchidometry **Laboratory:** • FSH, LH, testosterone (baseline at age 14 years and as clinically indicated in patients with delayed puberty and/or clinical signs and symptoms of testosterone deficiency) • Bone density evaluation in hypogonadal patients	Endocrine consultation for delayed puberty, persistently abnormal hormone levels, and hormonal replacement for hypogonadal patients
Precocious puberty: • Pubertal onset before age 9 years	**Radiation:** ≥ 18 Gy: • Cranial • Orbital/eye • Ear/infratemporal • Nasopharyngeal • Waldeyer's ring	**Host factors:** • Younger age at treatment	**Examination:** • Tanner staging • Testicular volume by Prader orchidometry **Laboratory:** • FSH, LH, testosterone as clinically indicated in patients with signs of accelerated pubertal progression and growth • Obtain x-ray for bone age in rapidly growing children	Endocrine consultation for accelerated puberty (puberty in boys age < 9 years)
Reduced fertility: • Oligospermia • Azoospermia	**Alkylating agents:** • Busulfan • Carmustine (BCNU) • Chlorambucil • Cyclophosphamide • Ifosfamide • Lomustine (CCNU) • Mechlorethamine • Melphalan • Procarbazine • Thiotepa • Carboplatin • Cisplatin • Dacarbazine (DTIC) • Temozolomide **Radiation:** • Any testicular dose • Flank/hemiabdomen • Whole abdomen, inverted Y, pelvic, prostate/bladder/iliac • Inguinal/femoral • TBI ≥ 30 Gy: • Cranial • Orbital/eye • Ear/infratemporal • Nasopharyngeal • Waldeyer's ring **Surgery:** • Orchiectomy • Hypothalamic pituitary axis	**Treatment factors:** • MOPP ≥ three cycles • Busulfan ≥ 600 mg/m^2 • Cyclophosphamide > 7.5 gm/m^2 • Ifosfamide ≥ 60 gm/m^2 • Multiple alkylating agents • Any alkylators combined with: testicular irradiation, pelvic irradiation, TBI • Radiation dose to testes: 1-3 Gy azoospermia may be reversible; 3-6 Gy azoospermia unlikely reversible **Host factors:** • Other comorbidities • Prescription medications	**Laboratory:** • Semen analysis as requested by patient; periodic evaluation over time is recommended because resumption of spermatogenesis can occur years after therapy • FSH, LH, testosterone as clinically indicated	Counsel regarding the need for contraception, because there is individual variability in gonadal toxicity after exposure to radiation and chemotherapy; recovery of fertility may occur years after therapy Reproductive endocrinology consultation for infertile couples interested in assisted reproductive technologies

(continued on following page)

Table 1. Risk Factors for and Assessment and Evaluation of Male Reproductive Complications After Treatment for Childhood, Adolescent, and Young Adult Cancers (continued)

Complication	Therapy	Risk Factors	Assessment	Evaluation
Sexual dysfunction: • Ejaculatory dysfunction • Erectile dysfunction	**Surgery:** • Neurosurgery: brain-hypothalamus/pituitary, spine • Pelvic/genitourinary surgery • Cystectomy **Radiation:** • Pelvic, genitourinary, bladder, cranial, spine	**Treatment factors:** • Spinal injury above the sacrum • Radiation dose ≥ 55 Gy to penile bulb in adult or ≥ 45 Gy in prepubertal child • Presacral or retroperitoneal resection or dissection **Host factors:** • Comorbid medical conditions • Hypogonadism	**History:** • Psychosexual • Sexual function (erections, ejaculation, nocturnal emissions, libido) • Medication use • Comorbidities **Examination:** • Genitourinary	Urologic consultation in patients with positive history

Abbreviations: FSH, follicle-stimulating hormone; LH, leutenizing hormone; MOPP, mechlorethamine, vincristine, procarbazine, prednisone; TBI, total-body irradiation; TLI, total-lymphoid irradiation.

deficiency and Leydig cell insufficiency, but no study to date has shown a measurable improvement with testosterone replacement therapy.[7,8,34] Furthermore, it is not clear if this clinical entity in young survivors predicts progression to overt Leydig cell failure over time.[26] Recommendations for ongoing screening and therapeutic interventions for survivors with Leydig cell insufficiency will be informed by further investigation.

PRECOCIOUS PUBERTY

Precocious puberty in boys is defined as pubertal onset before age 9 years.[27] Early onset of puberty results from premature activation of the HPG axis, resulting in the pulsatile secretion of GnRH, which in turn leads to stimulation of the testes by gonadotropins.

Risk Factors

Any survivor treated with radiation that includes the hypothalamus[35] (Table 1) is at risk for precocious puberty. Males younger at the time of irradiation and those who received doses ≥ 18 Gy are at greatest risk.[36]

Assessment

Increased testicular volume (≥ 4 mL) and other signs of puberty before age 9 years raise concern for precocious puberty. The COG-LTFU Guidelines recommend screening for precocious puberty in any survivor who received cranial radiation that included the hypothalamus (Table 1). Annual screening should include height, height velocity, and Tanner staging. A survivor with early signs of puberty is evaluated with early-morning serum LH, FSH, testosterone, and bone age (Table 1) and then referred to a pediatric endocrinologist. If any neurologic symptoms are present, brain magnetic resonance imaging should be considered to evaluate for other central pathologies associated with precocious puberty.[37,38]

Treatment

The goal of treatment for precocious puberty is to preserve adult height and delay further development of secondary sexual characteristics.[39] Premature testicular stimulation by gonadotropins can be blocked by administering GnRH analogs.[40] Therapeutic options include monthly depot injections of GnRH analogs or yearly implantation of a long-acting analog.[41,42] Treatment for precocious puberty continues until the normal age for puberty is reached.[43,44]

Additional Considerations

Boys who underwent cranial irradiation and have reduced testicular volume because of treatment-associated testicular germinal cell aplasia are difficult to assess for precocious puberty. For these survivors, monitoring with early-morning serum gonadotropins and testosterone should be considered.

REDUCED FERTILITY

Male fertility requires the intact function of the testes, HPG axis, and genitourinary organs. Survivors are at risk for reduced fertility if their treatment impairs the normal function of any component of the male reproductive system. Infertility can be secondary to impaired spermatogenesis from gonadotoxic therapy, gonadotropin deficiency resulting from CNS-directed therapy, or functional abnormalities of the genitourinary organs related to spinal/pelvic surgery or irradiation. The duration of post-treatment azoospermia secondary to gonadotoxic therapy is highly variable, and recovery of spermatogenesis may occur years after therapy.

Risk Factors

A primary risk factor for reduced fertility is alkylating agent–associated gonadal toxicity. The magnitude of risk is determined by the specific alkylating agent and the cumulative dose. Agents commonly used to treat pediatric malignancies and most often associated with oligo/azoospermia include mechlorethamine, cyclophosphamide, ifosfamide, procarbazine, busulfan, melphalan, and cisplatin (Table 1).[11,14,45-51] Young male survivors observed in the Childhood Cancer Survivor Study were less likely to sire a pregnancy after treatment with cyclophosphamide (hazard ratio [HR], 0.42; 95% CI, 0.31 to 0.57) or procarbazine (HR, 0.48; 95% CI, 0.26 to 0.87).[48] Although there is individual variation in risk of gonadotoxicity after exposure to alkylating agents, the cumulative dose likely to produce azoospermia has been established for most agents. Cumulative doses of cyclophosphamide > 5 to 7.5 gm/m^2 are associated with abnormal semen parameters, and azoospermia is consistently observed after total cyclophosphamide dose > 19 gm/m^2, ifosfamide > 60 gm/m^2, procarbazine > 4gm/m^2, busulfan > 600 mg/m^2, melphalan > 140 mg/m^2,

and cisplatin > 600 mg/m^2.[11,45,48-52] Alkylating agents used in combination have an additive effect on gonadotoxicity. Prepubertal status at diagnosis is not protective against alkylating agent germ cell toxicity.[11,48] Post-treatment azoospermia may be permanent, but recovery of normal spermatogenesis years after treatment is possible.[53,54]

The testicular germinal epithelium is especially sensitive to radiation. Spermatogenesis can be impaired by direct testicular irradiation, including total-body irradiation, or by scatter from other treatment fields including pelvic, bladder, inguinal/femoral, or abdominal/flank.[55] Impaired spermatogenesis is observed after testicular doses as low as 0.1 Gy, and recovery is unlikely after a single testicular dose exceeding 4 to 6 Gy.[9] The fertility analysis from the Childhood Cancer Survivor Study showed the likelihood of survivors siring a pregnancy decreased after radiation administered to the testes exceeding 7.5 Gy (HR, 0.12; 95% CI, 0.02 to 0.64).[48] Of note, small fractions of testicular radiation over long periods of time seem to be more toxic than an equivalent single-dose exposure.[56]

Gonadotropin deficiency, secondary to surgical disruption of the HPG axis or cranial radiation doses > 30 Gy, is also associated with reduced fertility.[19,57] Surgery or radiation to the genitourinary organs or associated neurovascular structures can reduce fertility secondary to erectile or ejaculatory dysfunction, including failure of emission or retrograde ejaculation (emission into the urinary bladder).[58,59]

Assessment

Fertility status in cancer survivors is most often determined by reduction in sperm count as measured by semen analysis using standardized methods.[60] Although semen analysis provides useful descriptive data including sperm count, motility, and morphology, it does not conclusively distinguish fertile from infertile men.[61] Abnormal semen analysis is suggestive of testicular germ cell damage, but azoospermia may also be secondary to ejaculatory dysfunction or hormone deficiencies in survivors at risk for those complications.[62,63] Evaluation for ejaculatory infertility includes differentiating retrograde ejaculation from anejaculation by analysis of alkalinized first morning urine or postejaculatory urine for sperm and fructose. Hormone-mediated azoospermia is diagnosed by measuring serum testosterone and gonadotropins (Table 1).

In addition to semen analysis, testicular volume and serum FSH can be used to assess potential fertility (Table 1).[11] Serum inhibin-B is also a marker for germ cell function; however, the COG-LTFU Guidelines do not recommend routinely screening with inhibin-B, because its additive value or superiority to other serum markers has not been established.[64] Men with an abnormal semen analysis should be counseled that it is not possible to predict when or whether spermatogenesis will recover, so contraception should be used if paternity is not desired.[65]

Treatment

Survivors with reduced fertility desiring biologic paternity should be referred to an infertility specialist. In the setting of normal testicular function, fertility secondary to central hypogonadism can potentially be restored with hormonal interventions.[31,32] In vitro fertilization (IVF) and intracytoplasmic sperm injection, an IVF procedure that uses a single sperm to fertilize an oocyte, are available to survivors with cryopreserved semen, oligospermia, and ejaculatory dysfunction to restore fertility. Neal et al[66] showed that pregnancy rates after IVF and intracytoplasmic sperm injection were similar in a small cohort of cancer survivor couples compared with couples without a cancer history. Testicular microdissection with sperm extraction (TESE) is a procedure to retrieve sperm from the testicular tissue of survivors with ejaculatory azoospermia who may have reduced but preserved spermatogenesis.[62,63] Viable sperm retrieval rates of 37% to 60% have been reported using the TESE procedure in the setting of azoospermia after chemotherapy.[62,63] In a study of 74 chemotherapy-associated azoospermic men, Hsiao et al[62] found sperm retrieval with TESE to be less successful after alkylating agent therapy or sarcoma diagnosis.

Additional Considerations

Although interventions to treat reduced fertility are widely available and offer reasonable rates of pregnancy, not all survivors access this technology. Obstacles that have been reported include health care providers' lack of knowledge about available reproductive technology, financial cost (because fertility treatments are not universally covered by health insurance), and an unwillingness to undergo medical procedures required for fertilization via assisted reproduction.[65-67] Options for parenthood, other than biologic paternity, include IVF using donor insemination and adoption.

SEXUAL DYSFUNCTION

Sexual dysfunction in the young cancer survivor, broadly defined as the inability to complete sexual intercourse, can be secondary to physical, emotional, and social changes associated with a cancer experience. The process of normal sexual function is complex, and dysfunction can result from diminished desire/interest/opportunity, arousal/erectile difficulty, and emission/ejaculatory/orgasmic problems. Psychosexual dysfunction can be the result of psychosocial challenges of a cancer experience, including mood disorders, fatigue, altered body image, social isolation, and delayed psychosexual development.[1,68-70] Physiologic sexual function depends on the complex interactions of genitourinary organs and associated neurovascular structures, all of which are vulnerable to damage from cancer therapy.[68,71-75] Surgery or irradiation of the pelvis or lumbar spine, treatment-associated hormonal insufficiencies, and medical comorbidities are possible etiologies for physiologic sexual dysfunction in cancer survivors. Although considerable research has been done on the prevalence and risk factors for sexual dysfunction in adult cancer survivors, few studies have been specific to childhood and young adult survivor populations. In a study of 1,084 testicular cancer survivors that included older adults, survivors reported a similar prevalence of sexual dysfunction (39%) compared with a normative sample; however, the younger group (age 20 to 39 years) reported more sexual problems than age-matched controls.[76] In a questionnaire study of 282 young male childhood cancer survivors (mean age, 27 years), 32% reported a problem in one or more areas of sexual function.[1]

Risk Factors

Cancer diagnosed during adolescence seems to be a risk factor for psychosexual sexual dysfunction.[69,70] A study of male and female childhood cancer survivors found that survivors treated as adolescents reported more social isolation and delays in achieving sexual milestones compared with both survivors treated at a younger age and the age-matched general population.[70] Childhood brain tumor survivors,

in particular, are reported to be at greater risk for psychosexual dysfunction, related to social isolation and delayed psychosexual development.[1,69] Poor health status was also found to be a risk factor for psychosexual dysfunction in young survivor populations.[1]

Risk factors for physiologic sexual dysfunction include prior treatment with pelvic or spinal surgery or irradiation, hormonal deficiency, increasing age, and emotional distress.[1,58,59,69,71,76,77] Erection is the result of increased penile blood flow regulated by somatic and autonomic nerves in response to psychologic or physical sexual stimulus, all of which are modulated by hormones. Erectile dysfunction (ED) is defined as the inability to achieve and maintain an erection sufficient to permit satisfactory sexual intercourse.[68] In a study by Zebrack et al,[1] 20% of young survivors self-reported a problem with ED. In a Swedish study by Sundberg et al,[69] 8% of sexually active young survivors reported ED compared with 3% of controls ($P = .15$). Possible treatment-associated etiologies for ED in childhood cancer survivors include pelvic or spinal radiation or surgery (neurovascular), central or primary hypogonadism (hormonal), and psychogenic ED resulting from emotional distress associated with the cancer experience.[68,71-74,78,79] Survivors with treatment-related medical comorbidities, and those taking prescription medications associated with ED, should also be considered at risk especially as they age into older adulthood.[80]

Ejaculation includes the emission of seminal fluid into the posterior urethara, ejection through the urethral meatus, and rhythmic contraction of the muscles of the pelvic floor, the sensation of orgasm. Ejaculation requires autonomically controlled contraction of the smooth muscles of the vas deferens, seminal vesicle, prostate, pelvic floor, and bladder neck.[81] Survivors are at increased risk for ejaculatory dysfunction (EjD) including failure of emission, retrograde emission into the bladder, orgasmic problems, orgasmic pain, and climacturia.[58,81-83] In their study of young adult childhood cancer survivors by Sundberg et al,[69] 10% reported orgasmic difficulty compared with 3% of controls ($P = .04$). Risk factors for EjD include pelvic or spinal surgery and radiation $\geq$ 45 Gy administered to pelvic fields. Presacral/retroperitoneal lymphnode dissections are associated with failure of emission and retrograde emission.[58,77,81-83] The incidence of neurogenic EjD after classic retroperitoneal lymph node dissection has been reduced with nerve-sparing techniques.[75]

Assessment

Because all survivors are at risk for psychosexual dysfunction related to their cancer experience, it is recommended that all adolescent and young adult survivors be assessed for sexual dysfunction as part of their follow-up care.[84] The assessment of sexual dysfunction in the childhood cancer survivor includes a thorough psychosexual history, sexual history, medical history, and physical examination including Tanner staging (Table 1). History should be obtained privately and include detailed questions about social relationships, body image, sexual experiences, libido, nocturnal emissions, spontaneous erections, masturbation, orgasm, and quality of ejaculate.[68,81]

Treatment

Survivors with psychosexual dysfunction can be referred for individual counseling with specific attention given to psychosexual development and social support.[84] If ED or EjD is diagnosed, the survivor should be referred to a urologist for evaluation. ED is typically treated using a stepwise approach, including addressing reversible causes such as hypogonadism.[85] First-line therapy includes oral phosphodiesterase type 5 inhibitors, followed by self-injectable penile vasoactive drugs, intraurethral alprostadil, and vacuum-assisted erection devices.[85] For survivors not satisfied with these interventions or survivors who have genitourinary abnormalities related to surgery or irradiation, penile prosthesis may be an option.[85] Depending on the etiology, treatment for EjD may include psychosexual counseling, pharmacotherapy, and possibly surgery.[81]

Additional Considerations

The increased prevalence of sexual dysfunction in the adolescent and young adult survivor population has recently been described.[1,69] Future investigations should be directed toward analyzing social, psychologic, and physiologic risk factors for sexual dysfunction in large cohorts of young survivors and designing interventions to reduce the incidence of this complication.

PRETREATMENT PRESERVATION OF REPRODUCTIVE HEALTH

Preservation of reproductive health has emerged as a priority for children, adolescents, and young adults diagnosed with cancer. Although not all reproductive complications can be prevented, strategies to minimize long-term issues by addressing reproductive concerns before treatment have improved outcomes for many survivors.

Treatment Modifications

Modifications in the dose and delivery of gonadotoxic therapy commonly used to treat childhood cancer have improved long-term reproductive outcomes. The evolution of the treatment of Hodgkin's lymphoma (HL) is a paradigm of efforts to reduce the risk of gonadal toxicity by adapting therapy to minimize male exposure to alkylating agents.[86,87] Pioneering work by Schellong et al[86] employed a nonalkylating agent chemotherapy regimen to treat boys with HL to preserve testicular germ cell function, which has since been adopted in other HL treatment protocols.[86,87] In a recent COG study for high-risk HL, survival was not compromised when boys received radiotherapy in place of alkylating agents with the aim of preserving future fertility.[88] Modifications in irradiation techniques to reduce dose to healthy tissue has improved long-term reproductive outcomes for survivors requiring treatment to pelvic fields. For example, proton radiotherapy used to treat pediatric pelvic rhabdomyosarcoma resulted in significant dose reduction to normal tissues compared with intensity-modulated radiotherapy.[89] Similarly, refinement of surgical techniques, such as nerve-sparing retroperitoneal surgery, has also been shown to preserve future reproductive capacity without sacrificing cure.[75]

Semen Cryopreservation

In 2006, the American Society of Clinical Oncology expert panel on fertility preservation recommended a discussion of fertility preservation options with all eligible patients before cancer therapy begins as part of the informed consent process.[45] Ideally, semen for cryopreservation should be collected by masturbation from all sexually mature males before the initiation of gonadotoxic therapy.[65] Males with reduced quantity or quality of sperm as a result of age or illness remain eligible for sperm banking, because future fertilization can be achieved from a single sperm using assisted reproductive technology,[63] and

sperm quality is not affected by duration of cryopreservation.[90] Peripubertal boys should also be considered eligible for semen collection if they report nocturnal emissions, masturbation with ejaculation, or have testicular volume ≥ 6 mL (Tanner stage 3), which roughly correlates with the onset of spermatogenesis.[91] If masturbation is not feasible or successful, alternative methods for semen collection including penile vibratory stimulation or intraoperative rectal electroejaculation are available in some clinical settings.[92,93] If a semen sample cannot be obtained by these methods, testicular biopsy with TESE can be used to obtain and preserve sperm for future fertility.[62]

Investigational Pretreatment Fertility Preservation

Pretreatment cryopreservation of testicular stem-cell tissue can be considered a fertility preservation option for prepubertal boys who do not yet produce spermatozoa. The success of future fertility using sperm generated from cryopreserved stem cells is not established; therefore, interventions described should be considered investigational. Pilot studies have confirmed that pretreatment testicular biopsy to obtain spermatogonial stem cells for cryopreservation is generally safe for patients and acceptable to parents.[94] Although autologous transplantation of cryopreserved testicular stem cells into survivors' testes seems to be a promising option for future fertility,[95-98] the safety and efficacy of this procedure have only been demonstrated in animal models.[99] Furthermore, boys with hematopoetic malignancies might not be eligible for this procedure because of the risk for recurrence from reintroducing malignant cells in cryopreserved testicular tissue.[100] Grafting cryopreserved spermatogonial stem cells into a host organism (xenograft) or in vitro spermatogenesis from cryopreserved spermatogonial stems might also be future options to preserve fertility for the youngest survivors.[101-103]

DISCUSSION

Semen cryopreservation, hormonal therapy, psychosexual counseling, and assisted reproduction are some of the many interventions available to optimize the long-term reproductive health of young male cancer survivors. The widespread application of these interventions depends, in large part, on the knowledge of the oncology care team about the risk for reproductive complications associated with specific cancer treatments and their comfort with discussing these often sensitive topics with young male patients and their families. The COG-LTFU Guidelines contain information about the reproductive risks associated with current curative cancer therapies. These guidelines are available to clinicians to inform discussion of fertility preservation before instituting therapy and to recommend ongoing evaluations for reproductive health concerns in the setting of follow-up care. Finally, ongoing research to both prevent and treat reproductive complications in males treated for childhood adolescent and young adult cancers is necessary to improve survivors' health and quality of life.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.
Employment or Leadership Position: None **Consultant or Advisory Role:** Nobuko Hijiya, Genzyme (C); Lillian Meacham, Pfizer (C) **Stock Ownership:** None **Honoraria:** Lillian Meacham, Pfizer **Research Funding:** Nobuko Hijiya, Genzyme **Expert Testimony:** None **Other Remuneration:** None

AUTHOR CONTRIBUTIONS

Conception and design: Lisa B. Kenney, Laurie E. Cohen, Monika L. Metzger, Eileen Duffey-Lind, Louis Constine, Daniel Green, Lillian Meacham
Collection and assembly of data: Lisa B. Kenney, Margarett Shnorhavorian, Barbara Lockart, Nobuko Hijiya, Louis Constine
Data analysis and interpretation: Lisa B. Kenney, Margarett Shnorhavorian
Manuscript writing: All authors
Final approval of manuscript: All authors

REFERENCES

1. Zebrack BJ, Foley S, Wittmann D, et al: Sexual functioning in young adult survivors of childhood cancer. Psychooncology 19:814-822, 2010
2. Zebrack BJ, Casillas J, Nohr L, et al: Fertility issues for young adult survivors of childhood cancer. Psychooncology 13:689-699, 2004
3. Hammond C, Abrams JR, Syrjala KL: Fertility and risk factors for elevated infertility concern in 10-year hematopoietic cell transplant survivors and case-matched controls. J Clin Oncol 25:3511-3517, 2007
4. Landier W, Wallace WH, Hudson MM: Long-term follow-up of pediatric cancer survivors: Education, surveillance, and screening. Pediatr Blood Cancer 46:149-158, 2006
5. Landier W, Bhatia S, Eshelman DA, et al: Development of risk-based guidelines for pediatric cancer survivors: The Children's Oncology Group Long-Term Follow-Up Guidelines from the Children's Oncology Group Late Effects Committee and Nursing Discipline. J Clin Oncol 22:4979-4990, 2004
6. Children's Oncology Group: Long-term follow-up guidelines for survivors of childhood, adolescent, and young adult cancers, version 3.0. http://ww.survivorshipguidelines.org
7. Greenfield DM, Walters SJ, Coleman RE, et al: Prevalence and consequences of androgen deficiency in young male cancer survivors in a controlled cross-sectional study. J Clin Endocrinol Metab 92: 3476-3482, 2007
8. Howell SJ, Radford JA, Adams JE, et al: The impact of mild Leydig cell dysfunction following cytotoxic chemotherapy on bone mineral density (BMD) and body composition. Clin Endocrinol (Oxf) 52:609-616, 2000
9. Rowley MJ, Leach DR, Warner GA, et al: Effect of graded doses of ionizing radiation on the human testis. Radiat Res 59:665-678, 1974
10. Howell SJ, Shalet SM: Effect of cancer therapy on pituitary-testicular axis. Int J Androl 25:269-276, 2002
11. Kenney LB, Laufer MR, Grant FD, et al: High risk of infertility and long term gonadal damage in males treated with high dose cyclophosphamide for sarcoma during childhood. Cancer 91:613-621, 2001
12. Muller J: Disturbance of pubertal development after cancer treatment. Best Pract Res Clin Endocrinol Metab 16:91-103, 2002
13. Sklar C: Reproductive physiology and treatment-related loss of sex hormone production. Med Pediatr Oncol 33:2-8, 1999
14. Brämswig JH, Heimes U, Heiermann E, et al: The effects of different cumulative doses of chemotherapy on testicular function: Results in 75 patients treated for Hodgkin's disease during childhood or adolescence. Cancer 65:1298-1302, 1990
15. Romerius P, Stahl O, Moell C, et al: Hypogonadism risk in men treated for childhood cancer. J Clin Endocrinol Metab 94:4180-4186, 2009

16. Eberhard J, Ståhl O, Cwikiel M, et al: Risk factors for post-treatment hypogonadism in testicular cancer patients. Eur J Endocrinol 158:561-570, 2008

17. Geenen MM, Bakker PJ, Kremer LC, et al: Increased prevalence of risk factors for cardiovascular disease in long-term survivors of acute lymphoblastic leukemia and Wilms tumor treated with radiotherapy. Pediatr Blood Cancer 55:690-697, 2010

18. Livesey EA, Hindmarsh PC, Brook CG, et al: Endocrine disorders following treatment of childhood brain tumours. Br J Cancer 61:622-625, 1990

19. Darzy KH, Shalet SM: Hypopituitarism following radiotherapy revisited. Endocr Dev 15:1-24, 2009

20. Izard MA: Leydig cell function and radiation: A review of the literature. Radiother Oncol 34:1-8, 1995

21. Howell SJ, Radford JA, Ryder WD, et al: Testicular function after cytotoxic chemotherapy: Evidence of Leydig cell insufficiency. J Clin Oncol 17:1493-1498, 1999

22. Shalet SM, Horner A, Ahmed SR, et al: Leydig cell damage after testicular irradiation for lymphoblastic leukaemia. Med Pediatr Oncol 13:65-68, 1985

23. Blatt J, Sherins RJ, Niebrugge D, et al: Leydig cell function in boys following treatment for testicular relapse of acute lymphoblastic leukemia. J Clin Oncol 3:1227-1231, 1985

24. Kiserud CE, Fosså A, Bjøro T, et al: Gonadal function in male patients after treatment for malignant lymphomas, with emphasis on chemotherapy. Br J Cancer 100:455-463, 2009

25. Lin WW, Kim ED, Quesada ET, et al: Unilateral testicular injury from external trauma: Evaluation of semen quality and endocrine parameters. J Urol 159:841-843, 1998

26. Bandak M, Aksglaede L, Juul A, et al: The pituitary-Leydig cell axis before and after orchiectomy in patients with stage I testicular cancer. Eur J Cancer 47:2585-2591, 2011

27. Marshall WA, Tanner JM: Variations in the pattern of pubertal changes in boys. Arch Dis Child 45:13-23, 1970

28. Cohen LE: Endocrine late effects of cancer treatment. Endocrinol Metab Clin North Am 34:769-789, 2005

29. Dattani MT, Hindmarsh PC: Normal and abnormal puberty, in Brook CG, Clayton P, Brown RS (eds): Clinical Pediatric Endocrinology (ed 5). Malden, MA, Blackwell Publishing, 2005, pp 183-210

30. Bhasin S, Cunningham GR, Hayes FJ, et al: Testosterone therapy in men with androgen deficiency syndromes: An Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 95:2536-2559, 2010

31. Delemarre EM, Felius B, Delemarre-van de Waal HA: Inducing puberty. Eur J Endocrinol 159: S9-S15, 2008 (suppl 1)

32. Delemarre-van de Waal HA: Application of gonadotropin releasing hormone in hypogonadotropic hypogonadism: Diagnostic and therapeutic aspects. Eur J Endocrinol 151:U89–U94, 2004 (suppl 3)

33. Barrio R, de Luis D, Alonso M, et al: Induction of puberty with human chorionic gonadotropin and follicle-stimulating hormone in adolescent males with hypogonadotropic hypogonadism. Fertil Steril 71:244-248, 1999

34. Howell SJ, Radford JA, Adams JE, et al: Randomized placebo-controlled trial of testosterone replacement in men with mild Leydig cell insufficiency following cytotoxic chemotherapy. Clin Endocrinol (Oxf) 55:315-324, 2001

35. Oberfield SE, Soranno D, Nirenberg A, et al: Age at onset of puberty following high-dose central nervous system radiation therapy. Arch Pediatr Adolesc Med 150:589-592, 1996

36. Ogilvy-Stuart AL, Clayton PE, Shalet SM: Cranial irradiation and early puberty. J Clin Endocrinol Metab 78:1282-1286, 1994

37. Carel JC, Leger J: Clinical practice: Precocious puberty. N Engl J Med 358:2366-2377, 2008

38. Mul D, Hughes IA: The use of GnRH agonists in precocious puberty. Eur J Endocrinol 159:S3-S8, 2008 (suppl 1)

39. Carel JC, Lahlou N, Roger M, et al: Precocious puberty and statural growth. Hum Reprod Update 10:135-147, 2004

40. Neely EK, Hintz RL, Parker B, et al: Two-year results of treatment with depot leuprolide acetate for central precocious puberty. J Pediatr 121:634-640, 1992

41. Crowley WF Jr, Comite F, Vale W, et al: Therapeutic use of pituitary desensitization with a long-acting lhrh agonist: A potential new treatment for idiopathic precocious puberty. J Clin Endocrinol Metab 52:370-372, 1981

42. Eugster EA, Clarke W, Kletter GB, et al: Efficacy and safety of histrelin subdermal implant in children with central precocious puberty: A multicenter trial. J Clin Endocrinol Metab 92:1697-1704, 2007

43. Oostdijk W, Rikken B, Schreuder S, et al: Final height in central precocious puberty after long term treatment with a slow release GnRH agonist. Arch Dis Child 75:292-297, 1996

44. Carel JC, Eugster EA, Rogol A, et al: Consensus statement on the use of gonadotropin-releasing hormone analogs in children. Pediatrics 123:e752–e762, 2009

45. Lee SJ, Schover LR, Partridge AH, et al: American Society of Clinical Oncology recommendations on fertility preservation in cancer patients. J Clin Oncol 24:2917-2931, 2006

46. Clark ST, Radford JA, Crowther D, et al: Gonadal function following chemotherapy for Hodgkin's disease: A comparative study of MVPP and a seven-drug hybrid regimen. J Clin Oncol 13:134-139, 1995

47. Shafford EA, Kingston JE, Malpas JS, et al: Testicular function following the treatment of Hodgkin's disease in childhood. Br J Cancer 68:1199-1204, 1993

48. Green DM, Kawashima T, Stovall M, et al: Fertility of male survivors of childhood cancer: A report from the Childhood Cancer Survivor Study. J Clin Oncol 28:332-339, 2010

49. Aubier F, Flamant F, Brauner R, et al: Male gonadal function after chemotherapy for solid tumors in childhood. J Clin Oncol 7:304-309, 1989

50. Meistrich ML, Wilson G, Brown BW, et al: Impact of cyclophosphamide on long-term reduction in sperm count in men treated with combination chemotherapy for Ewing and soft tissue sarcomas. Cancer 70:2703-2712, 1992

51. Williams D, Crofton PM, Levitt G: Does ifosfamide affect gonadal function? Pediatr Blood Cancer 50:347-351, 2008

52. Hobbie WL, Ginsberg JP, Ogle SK, et al: Fertility in males treated for Hodgkins disease with COPP/ABV hybrid. Pediatr Blood Cancer 44:193-196, 2005

53. Buchanan JD, Fairley KF, Barrie JU: Return of spermatogenesis after stopping cyclophosphamide therapy. Lancet 2:156-157, 1975

54. Meistrich ML, Chawla SP, Da Cunha MF, et al: Recovery of sperm production after chemotherapy for osteosarcoma. Cancer 63:2115-2123, 1989

55. Fraass BA, Kinsella TJ, Harrington FS, et al: Peripheral dose to the testes: The design and clinical use of a practical and effective gonadal shield. Int J Radiat Oncol Biol Phys 11:609-615, 1985

56. Apperley JF, Reddy N: Mechanism and management of treatment-related gonadal failure in recipients of high dose chemoradiotherapy. Blood Rev 9:93-116, 1995

57. Gleeson HK, Shalet SM: The impact of cancer therapy on the endocrine system in survivors of childhood brain tumours. Endocr Relat Cancer 11: 589-602, 2004

58. Kubota M, Yagi M, Kanada S, et al: Long-term follow-up status of patients with neuroblastoma after undergoing either aggressive surgery or chemotherapy: A single institutional study. J Pediatr Surg 39:1328-1332, 2004

59. Macedo A Jr, Ferreira PV, Barroso U Jr, et al: Sexual function in teenagers after multimodal treatment of pelvic rhabdomyosarcoma: A preliminary report. J Pediatr Urol 6:605-608, 2010

60. World Health Organization Laboratory Manual for Human Semen and Cervical Mucus Interaction (ed 4). Cambridge, UK, Cambridge University Press, 1999

61. Guzick DS, Overstreet JW, Factor-Litvak P, et al: Sperm morphology, motility, and concentration in fertile and infertile men. N Engl J Med 345:1388-1393, 2001

62. Hsiao W, Stahl PJ, Osterberg EC, et al: Successful treatment of postchemotherapy azoospermia with microsurgical testicular sperm extraction: The Weill Cornell experience. J Clin Oncol 29:1607-1611, 2011

63. Damani MN, Master V, Meng MV, et al: Postchemotherapy ejaculatory azoospermia: Fatherhood with sperm from testis tissue with intracytoplasmic sperm injection. J Clin Oncol 20:930-936, 2002

64. Kumanov P, Nandipati K, Tomova A, et al: Inhibin B is a better marker of spermatogenesis than other hormones in the evaluation of male factor infertility. Fertil Steril 86:332-338, 2006

65. Ginsberg JP, Ogle SK, Tuchman LK, et al: Sperm banking for adolescent and young adult cancer patients: Sperm quality, patient, and parent perspectives. Pediatr Blood Cancer 50:594-598, 2008

66. Neal MS, Nagel K, Duckworth J, et al: Effectiveness of sperm banking in adolescents and young adults with cancer: A regional experience. Cancer 110:1125-1129, 2007

67. Schover LR, Brey K, Litchtin A, et al: Oncologists' attitudes and practices regarding banking sperm before cancer treatment. J Clin Oncol 20: 1890-1897, 2002

68. Lue TF: Erectile dysfunction. N Engl J Med 342:1802-1813, 2000

69. Sundberg KK, Lampic C, Arvidson J, et al: Sexual function and experience among long-term survivors of childhood cancer. Eur J Cancer 47:397-403, 2010

70. van Dijk EM, van Dulmen-den Broeder E, Kaspers GJ, et al: Psychosexual functioning of childhood cancer survivors. Psychooncology 17:506-511, 2008

71. Kiserud CE, Schover LR, Dahl AA, et al: Do male lymphoma survivors have impaired sexual function? J Clin Oncol 27:6019-6026, 2009

72. Lackner J, Schatzl G, Koller A, et al: Treatment of testicular cancer: Influence on pituitary-gonadal axis and sexual function. Urology 66: 402-406, 2005

73. Huddart RA, Norman A, Moynihan C, et al: Fertility, gonadal and sexual function in survivors of testicular cancer. Br J Cancer 93:200-207, 2005

74. Maas R, Schwedhelm E, Albsmeier J, et al: The pathophysiology of erectile dysfunction related to endothelial dysfunction and mediators of vascular function. Vasc Med 7:213-225, 2002

75. Jacobsen KD, Ous S, Waehre H, et al: Ejaculation in testicular cancer patients after post-chemotherapy retroperitoneal lymph node dissection. Br J Cancer 80:249-255, 1999

76. Dahl AA, Bremnes R, Dahl O, et al: Is the sexual function compromised in long-term testicular cancer survivors? Eur Urol 52:1438-1447, 2007

77. Half E, Bercovich D, Rozen P: Familial adenomatous polyposis. Orphanet J Rare Dis 4:22, 2009

78. Araujo AB, Durante R, Feldman HA, et al: The relationship between depressive symptoms and male erectile dysfunction: Cross-sectional results from the Massachusetts Male Aging Study. Psychosom Med 60:458-465, 1998

79. Tal R, Heck M, Teloken P, et al: Peyronie's disease following radical prostatectomy: Incidence and predictors. J Sex Med 7:1254-1261, 2010

80. Billups KL, Bank AJ, Padma-Nathan H, et al: Erectile dysfunction is a marker for cardiovascular disease: Results of the minority health institute expert advisory panel. J Sex Med 2:40-50, 2005; discussion 50-52

81. Rowland D, McMahon CG, Abdo C, et al: Disorders of orgasm and ejaculation in men. J Sex Med 7:1668-1686, 2010

82. Choi JM, Nelson CJ, Stasi J, et al: Orgasm associated incontinence (climacturia) following radical pelvic surgery: Rates of occurrence and predictors. J Urol 177:2223-2226, 2007

83. Fosså SD, Oldenburg J, Dahl AA: Short- and long-term morbidity after treatment for testicular cancer. BJU Int 104:1418-1422, 2009

84. Canada AL, Schover LR, Li Y: A pilot intervention to enhance psychosexual development in adolescents and young adults with cancer. Pediatr Blood Cancer 49:824-828, 2007

85. The process of care model for evaluation and treatment of erectile dysfunction: The Process of Care Consensus Panel. Int J Impot Res 11:59-70, 1999; discussion 70-74

86. Schellong G, Pötter R, Brämswig J, et al: High cure rates and reduced long-term toxicity in pediatric Hodgkin's disease: The German-Austrian multicenter trial DAL-HD-90—The German-Austrian Pediatric Hodgkin's Disease Study Group. J Clin Oncol 17:3736-3744, 1999

87. Mauz-Körholz C, Hasenclever D, Dörffel W, et al: Procarbazine-free OEPA-COPDAC chemotherapy in boys and standard OPPA-COPP in girls have comparable effectiveness in pediatric Hodgkin's lymphoma: The GPOH-HD-2002 study. J Clin Oncol 28:3680-3686, 2010

88. Kelly KM, Sposto R, Hutchinson R, et al: BEACOPP chemotherapy is a highly effective regimen in children and adolescents with high-risk Hodgkin lymphoma: A report from the Children's Oncology Group. Blood 117:2596-2603, 2011

89. Cotter SE, Herrup DA, Friedmann A, et al: Proton Radiotherapy for Pediatric Bladder/Prostate Rhabdomyosarcoma: Clinical Outcomes and Dosimetry Compared to Intensity-Modulated Radiation Therapy. Int J Radiat Oncol Biol Phys 81:1367-1373, 2010

90. Horne G, Atkinson AD, Pease EH, et al: Live birth with sperm cryopreserved for 21 years prior to cancer treatment: Case report. Hum Reprod 19: 1448-1449, 2004

91. Hagenäs I, Jørgensen N, Rechnitzer C, et al: Clinical and biochemical correlates of successful semen collection for cryopreservation from 12-18-year-old patients: A single-center study of 86 adolescents. Hum Reprod 25:2031-2038, 2010

92. Schmiegelow ML, Sommer P, Carlsen E, et al: Penile vibratory stimulation and electroejaculation before anticancer therapy in two pubertal boys. J Pediatr Hematol Oncol 20:429-430, 1998

93. Wallace WH, Anderson RA, Irvine DS: Fertility preservation for young patients with cancer: Who is at risk and what can be offered? Lancet Oncol 6:209-218, 2005

94. Ginsberg JP, Carlson CA, Lin K, et al: An experimental protocol for fertility preservation in prepubertal boys recently diagnosed with cancer: A report of acceptability and safety. Hum Reprod 25:37-41, 2010

95. Keros V, Hultenby K, Borgström B, et al: Methods of cryopreservation of testicular tissue with viable spermatogonia in pre-pubertal boys undergoing gonadotoxic cancer treatment. Hum Reprod 22:1384-1395, 2007

96. Schlatt S, von Schönfeldt V, Schepers AG: Male germ cell transplantation: An experimental approach with a clinical perspective. Br Med Bull 56:824-836, 2000

97. Feng LX, Chen Y, Dettin L, et al: Generation and in vitro differentiation of a spermatogonial cell line. Science 297:392-395, 2002

98. Schlatt S, Ehmcke J, Jahnukainen K: Testicular stem cells for fertility preservation: Preclinical studies on male germ cell transplantation and testicular grafting. Pediatr Blood Cancer 53:274-280, 2009

99. Zhang Z, Renfree MB, Short RV: Successful intra- and interspecific male germ cell transplantation in the rat. Biol Reprod 68:961-967, 2003

100. Jahnukainen K, Hou M, Petersen C, et al: Intratesticular transplantation of testicular cells from leukemic rats causes transmission of leukemia. Cancer Res 61:706-710, 2001

101. Revel A, Revel-Vilk S: Pediatric fertility preservation: Is it time to offer testicular tissue cryopreservation? Mol Cell Endocrinol 282:143-149, 2008

102. Schlatt S, Honaramooz A, Boiani M, et al: Progeny from sperm obtained after ectopic grafting of neonatal mouse testes. Biol Reprod 68:2331-2335, 2003

103. Sadri-Ardekani H, Mizrak SC, van Daalen SK, et al: Propagation of human spermatogonial stem cells in vitro. JAMA 302:2127-2134, 2009

